METANALYSIS CRITICAL OF BLOOD ALTERNATIVE PRODUCT CHALLENGED



Hemopure researcher, the University of Maryland's Professor Colin Mackenzie, and the manager of Hemopure in South Africa, Dr Mandisa Maholwana.

Picture: Chris Bateman

A 'deeply flawed' metanalysis of the life-saving interim blood alternative, Hemopure, published in an American scientific journal this April[1] has led to at least one province and hospitals elsewhere avoiding its use – to their detriment.

Hemopure is purified haemoglobin in a sterile solution that acts as an oxygen bridge when compatible red blood cells are not readily available. It has been shown to save the lives of 42% of haemorrhaging and severely anaemic patients who would otherwise have died, and has no lasting side-effects.[2] The product is stable at room temperature, has a shelf life of 3 years and requires no blood cross-matching.

It is approved for 'compassionate use' in the USA, and licensed for acute anaemia and delaying the need for predictable blood transfusion (in adult surgical patients) in South Africa. South Africa is the world's leader in all-cause trauma mortality, making the product highly relevant locally.

Izindaba spoke to the man who conducted the seminal research, University of Maryland Professor Colin Mackenzie, when he was in Cape Town this August to attend the Combined Congress of the Critical Care Society of South Africa.

Mackenzie and the manager of Hemopure in South Africa, Dr Mandisa Maholwana, revealed that since the controversial metanalysis appeared in the *Journal of the American Medical Association (JAMA)*,[1] in April, usage reticence had crept in. Maholwana said the KwaZulu-Natal health authorities had ordered doctors to stop using Hemopure while in Gauteng: 'We recently had a case where the clinicians weren't allowed to use it, so they sourced it from a private hospital'.

Thumbs up from Jehovah's Witnesses

Both Hemopure (created using haemoglobin polymer synthesised from bovine haemoglobin) and another similar product, Polyheme (derived from human haemoglobin), are unconditionally accepted by Jehovah's Witnesses. Members of this church have long prompted ethical controversy by refusing potentially life-saving blood transfusions.

Dr Anthony Reed, the provincial co-ordinating clinician for anaesthetic services in the Western Cape, said he encountered about 'one Jehovah's Witness patient every six months' in clinical practice. Reed spoke favourably of Hemopure's applications.

Maholwana said they were beginning to see the pharmaceutical and therapeutic committees (PTCs) of individual hospitals rejecting Hemopure, although luckily this unfounded reticence had yet to filter through to the national health department.

'We're really worried about the rural areas, where urgently obtaining the correct type of blood is often so difficult or sometimes even impossible,' she observed.

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'We're really worried about the rural areas, where urgently obtaining the correct type of blood is often so difficult or sometimes even impossible,' she observed. The longest recorded period a patient has been kept alive (and survived) in South Africa on Hemopure is 19 hours. In the USA a patient with autoimmune haemolytic anaemia and a red cell haemoglobin 0.8 g/dl was kept alive for 19 days, further attesting to the safety of the drug. Published research shows that 96.3% of patients can avoid blood transfusion for 24 hours by using Hemopure.[2] Mackenzie emphasised that correct use and repeat dosages were critical for optimal outcomes.

He said the metanalysis[1] of haemoglobin-based oxygen carriers combined 5 different products and pooled 22 Hemopure studies using different methodologies and different settings on heterogeneous patient populations with differing controls. It incorrectly concluded that there was an increase in mortality and myocardial infarction for all these products, which is not the case with Hemopure.

'You can't do a metanalysis like that. They pooled high mortality and low mortality trials. If, as the metanalysis suggested, all these products were the same, then they should have examined dose response effects, but this was not done because of major heterogeneities among the trials,' he added.

Mackenzie said he had just returned from a major hospital in Bloemfontein where clinicians spoke of losing three patients postpartum due to haemorrhage, with no available blood in just the past 2 months. 'So you can imagine the cost in live births of not using Hemopure,' he added.

Mackenzie is also the co-author of the largest single published study on the use of haemoglobin-based oxygen carriers in comparison to packed red cells for elective surgery (680 patients), published in June of this year in the *Journal of Trauma, Injury, Infection and Critical Care*. Mortality for moderate use (3 units of packed red blood cells or 10 units of Hemopure) was found to be 1% in both cohorts, and serious adverse events were 0.14 per patient.

Highly effective interim measure

This study found that Hemopure eliminated transfusion in the majority of subjects and that patients under 80 years old with moderate clinical needs could safely avoid transfusion when treated with up to 10 units of Hemopure.[3]

Mackenzie said their best counter to what he terms 'political issues that have been raised that have nothing to do with science' was the inexorable publication of peer-reviewed gold standard research. He revealed that the US military was very keen to support his team's application to use Hemopure in a resuscitation study of combat casualties in Iraq (alternative oxygen carriers have their research origins in the US military in the 1950s).

'The money was all there, but the Food & Drug Administration (FDA) had safety concerns related to what they called hypertension' (what Mackenzie prefers to call 'transient elevation of blood pressure').

In a public FDA hearing, the voting revealed a dramatic split – all the clinicians voted in favour and all the 'blood bankers and non-clinicians' voted against. Mackenzie said the elevation of systolic blood pressure of 23 mm of mercury on the first infusion of Hemopure and 10 mm on subsequent infusions was 'clinically irrelevant'.

'The blood bank people think it's dangerous, yet nobody's ever done a clinical trial of blood! Hemopure simply fills the gap until blood becomes available,' he stressed.

Prompted to share the costs of Hemopure, Maholwana revealed that the single exit price was R3 500 per unit (VAT incl.) in the public sector and R5 800 (VAT incl.) in the private sector.

Pricing comparisons 'impossible'

Maholwana said it was 'virtually impossible' to establish the comparative cost of blood as the hidden costs of transfusion, collection, cross-matching, screening, storage, delivery and restocking every 6 weeks remained hidden, especially in the public sector. 'I've been to two different hospitals and got two entirely different unit prices – they pay the blood bank and the lab… they just don't know,' she said.

Mackenzie said what the publication of the metanalysis in the *JAMA* had done was 'polarise people into believing that all haemoglobin oxygen carriers are the same, which they are not'. Given the critical blood shortage in many countries, especially around festive seasons, 'it's important that we remember that if you don't have blood, there's nothing else. People should open up their minds,' he added.

In the USA the projected shortfall of blood by the year 2014 was 4 million units, a potent illustration of just how important this product application may become.[4]

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1. Natanson C, Wolfe S. *JAMA* 2008; 299: 2324-2326.
2. Moon-Massat PF, Mackenzie C, Shander A, Greenburg AG. Paper presented at the Critical Care and Thoracic Society Conference, Cape Town, August 2008.
3. *Journal of Trauma, Injury, Infection and Critical Care* 2008; 64 (6): 1484-1497.
4. Vamvakas EC. Epidemiology of red cell utilization. *Transfus Med Rev* 1996; 19: 44-61.

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retirement savings for life crises when they leave their employer.

'South Africans often withdraw their savings before retirement to educate their kids, provide income in times of illness and death or buy a small business. Fear of not having access to these savings in future is currently worsening the outflow,' she explains.

This is aggravated by HIV and AIDS and the accompanying stigma, fuelling unemployment and draining 34% of household expenditure in affected families. While Metropolitan was 'very sensitive' to the interests of low-income earners who need access to savings for life crises, it had to emphasise the crucial importance of preserving funds, she said.

Retirement funds used for emergencies

Many middle- and higher-income classes in South Africa also withdrew from their retirement savings during their working lives, leading to inadequate financial protection in retirement. It was 'common knowledge' in the insurance industry that if you cashed in the retirement savings of the first 10 years of your career, it would reduce your pension by around 40%.

'We want to reduce people's dependency on government when they retire by forcing them to save throughout their lifetime. Yet if they do that and end up not having enough money to look after the sick and jobless on their way there, it will increase the social burden on the state.'

Nicolay compared the R6 000 cost of a year's ART versus paying out, for example, R45 000 in death benefits for a person earning R15 000 a year.

Fortunately, government recognised this and spoke in its discussion papers of the urgent need to broaden social security while encouraging job creation and protecting disposable income. When it came to HIV and AIDS, it was far cheaper to treat someone with antiretroviral therapy (ART) than to pay out a death benefit (typically 3 times one's annual salary). Nicolay compared the R6 000 cost of a year's ART versus paying out, for example, R45 000 in death benefits for a person earning R15 000 a year. Added to this were the medical costs of treating opportunistic infections, lower productivity and higher unemployment.

Upscaling prevention and treatment vital

'It has to be cost effective to invest heavily in prevention and treatment of employed people instead of giving them a fund that will pay out millions in death and disability benefits. The NSSF will then be able to focus more on saving and preservation for old age, as was the original intention,' she adds.

Nicolay hit headlines 2 years ago when she outlined her 'four seasons' 2025 AIDS scenarios with the 'Winter of discontent', featuring weak self-serving leadership, high crime and an AIDS response involving fake cures and corrupt systems.

She predicted continuous deaths in the workplace leading to companies closing down, with only 1 in 5 South Africans knowing their status by 2010 and the life expectancy remaining at 50 years. In stark contrast, the 2025 'Summer for all people' featured strong collaborative leadership committed to a developmental society, led by government, a focus on prevention with treatment, and care. Proactive business would be sustainable as the epidemic shrank, with up to 60% of people knowing their status by 2010 and only 7% of the employed population being infected by 2025.

An estimated 20% of all South Africans between the ages of 20 and 64 are currently HIV positive.

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